lost (Fig. 1*C*). If the cell response was averaged many times (up to 100 times) a peak of activity could sometimes be observed to correspond with the minimum or the maximum intensity of light, according to the cell type ("off cells" or "on cells," respectively). The shape of the response, however, remained completely chaotic. An example of these results is shown in Fig. 1. Control experiments showed that the response of the retinal ganglion cell to sine-wave stimulation is not affected by either the waking or the sleeping state. This observation shows that the striking difference observed with LGB units is probably due to extraretinal influences acting upon the LGB neurons during sleep.

The inability of LGB units to follow sine-wave photic stimulation during synchronized sleep might be explained in two different, but not mutually exclusive, ways. (i) During spontaneous sleep, unit firing is clustered in irregular bursts. The "noise" of the carrier (spontaneous activity) could be so high as to mask modulation from the retina. Experiments in which the cell response was averaged up to 100 times suggest that noise is not the only factor. (ii) The response of LGB units to retinal volleys is markedly decreased during synchronized sleep, as shown by observations made in the same experimental situation with single flashes of light (*5*). Even with a threefold increase in the amplitude of the intensity oscillation of the photic stimulus, we were unable to obtain, during synchronized sleep, the close correspondence between stimulus and rate of firing which can be observed constantly during wakefulness.

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References and Notes

1. G. W. Hughes and L. Maffei, *Atti Accad. Nazl. Lincei, Rend. Classe Sci. Fls. Mat. Nat.* **37**, 328 (1965).
2. G. W. Hughes and L. Maffei, in preparation.
3. C. Batini, G. Moruzzi, M. Palestini, G. F. Rossi, A. Zanchetti, *Arch. Ital. Biol.* **97**, 1 (1959).
4. D. H. Hubel, *J. Physiol. London* **150**, 91 (1960).
5. L. Maffei and G. Rizzolatti, *Ach. Ital. Biol.*, in press.
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Melphalan and Antigenic Type of Bence Jones Proteins in Myeloma

Bergsagel, Migliore, and Griffith report [*Science* **148**, 376, 1965] that none of nine myeloma patients with λ-type (type II) Bence-Jones (BJ) proteinuria responded to melphalan (L-phenylalanine mustard), whereas all 11 patients with κ-type (type I) BJ protein showed objective improvement. They conclude that the biochemical differences between these two types of myeloma cells may be related to their respective chemotherapeutic responsiveness. Results in our clinic, however, are at complete variance with those of Bergsagel *et al.* Using the same criteria for evaluating drug efficacy, we have discerned no difference in the responsiveness to melphalan of κ-BJ and λ-BJ producers. Objective remissions as evidenced by diminished BJ-proteinuria, improved hematologic status, and performance status have been observed in 38 of 45 myeloma patients treated with melphalan for 6 months or longer; three of the 38 had λ-BJ as their only protein abnormality. One case with κ-BJ was considered a treatment failure. Of the three patients with λ-BJ proteinuria who responded to melphalan, all showed reduction in BJ proteinuria of over 10 g/24 hr, increase in hemoglobin of over 2 g percent, and major pain relief and functional improvement, and one showed partial skeletal recalcification. Comparable results were obtained in our patients with κ-BJ, three of four of whom responded to melphalan. Similarly, we have found no differences in the responsiveness of patients with γG or γA globulin abnormalities with κ or λ L-chain determinants, with or without associated BJ proteinuria.

The reason for the failure of the Southwest Cancer Chemotherapy Study Group to observe remissions in any of their nine λ-BJ cases is obscure but may be related to the therapeutic protocols employed. The authors state that two different dosage schedules—A and B—were used, but do not report how many cases in each group were on schedule A and how many on schedule B. Since schedule A was apparently found to be excessive and associated with considerable toxicity, it may have contributed to poor results in certain cases. In our series, all patients received an initial course of 10 mg/day for 7 to 10 days; therapy was then interrupted for 3 to 8 weeks, until the maximum leukopenia had passed, at which time continuous maintenance therapy with 2 mg/day was instituted. On this dosage schedule, serious toxicity has not been encountered.

Two additional aspects of management are also deserving of emphasis: first, the importance of maintaining adequate hydration, particularly in cases with hypercalcemia and BJ proteinuria, and, second, the value of encouraging ambulation and exercise in the long-term management program. In this latter regard, two of our λ-BJ patients responding to melphalan have progressed from initially serious incapacitation, hypercalcemia, anemia, and bed-chair status, to regular golfing (18 to 27 holes, "in the 90's") in one case, and, in the other, to a program of daily pool-swimming (100 to 150 yards). Obviously, these ancillary aspects of management must be individualized to the capacities of individual patients, and, unfortunately, this tailoring is virtually impossible in a cooperative group study with a rigid protocol.

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We are unable to confirm the observations of Bergsagel, Migliore, and Griffith that patients producing only Bence-Jones κ proteins consistently do well on melphalan therapy, and that patients producing only Bence-Jones λ proteins do not respond to the drug. At Memorial and James Ewing Hospitals over the past 2 years we have treated 40 patients with Alkeran. To date 6 of our 27 adequately treated patients have had excellent subjective and objective responses to the drug, according to criteria of evaluation similar to those of Bergsagel *et al.* Under our terminology these six patients have had "IA" responses, comparable to Bergsagel's "significant" response. Of these six, two excreted Bence-Jones protein only. Both were of the λ type. Twelve of our adequately treated patients have had no response whatsoever to Alkeran. All have been observed on therapy for a minimum of 3 months. Six excrete Bence-Jones only. Four of these have λ L-chains and two have κ L-chains.

Thus, our data are strikingly different from those of Bergsagel *et al.* with re-

spect to the relation between κ or λ L-chains and response to therapy. We have not been able to find any clue through analysis of the abnormal myeloma proteins to help us predict survival time or response to therapy of any kind.

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In our report we said, "The concept that tumor-cell differentiation may influence the response to chemotherapy needs to be explored further, and considered in future therapeutic trials in myeloma." We were, in effect, asking other investigators to review their data and to plan future studies to confirm, or refute, our findings. Therefore, although we are a little deflated, we welcome the letters of Osserman and of Lee *et al.* The recording of objective improvement in five of ten patients producing only λ-BJP and of the failure of three of six patients producing only κ-BJP to improve following melphalan therapy certainly presents a different frequency of response from what we have reported. These data clearly indicate that the correlation of melphalan response to these proteins types is not absolute; but they are still inadequate to disprove the thesis that patients producing only κ-BJP respond more frequently than those producing only λ-BJP.

The differences in the frequency of response to melphalan observed by Osserman, Lee *et al.*, and by the Southwest Cancer Chemotherapy Study Group (SWCCSG) may be due to many factors, so that it is difficult to compare the three series. Two important differences are the dosage schedules employed and the selection of evaluable patients. Osserman only evaluated the response of patients treated for 6 months or more, and Lee *et al.* report on "adequately treated" patients (27 of 40) observed on therapy for a minimum of 3 months, whereas we evaluated the response of all patients followed for at least 3 weeks. We found that 6 to 9 months of treatment were required for optimum improvement, but in most cases it was possible to rate the response within 3 weeks after the first course of the drug (1.0 mg/kg in 4 days). In our series, 14 of the total group of 91 (15.4 percent), 2 of 12 patients (16.6 percent) producing only κ-BJP, and 3 of 9 patients (33.3 percent) producing only λ-BJP, died within the first 6 months. The elimination of patients who die early would probably result in the loss of more nonresponders than responders from the series of Osserman and of Lee *et al.*; this makes their series different from ours.

Osserman suggests that the excessive toxicity of our melphalan dosage schedule A may have contributed to our poor results with patients producing only λ-BJP. This is very unlikely; none of the patients treated with schedule A or B died as a result of hematological toxicity, and all of the patients excreting only κ- and λ-BJP were treated with schedule B. The mean melphalan dose rate (mg/kg/month) was 0.59 for the κ-BJP group and 0.53 for the λ-BJP group; these dose rates are not significantly different.

Even if we assume that the different melphalan dosage schedules employed by Osserman, Lee *et al.*, and the SWCCSG did not influence the results, and also assume that there were no early deaths in the Osserman or Lee *et al.* series, there is still convincing evidence that patients producing only κ-BJP respond more frequently (14 of 17) than those producing only λ-BJP (5 of 19), when the results of the three series are combined.

We believe that a well-designed prospective study, with a larger number of patients, will be required to confirm or refute our report, for the patients should be unselected and treated in a comparable fashion, and the results should be analyzed carefully from many points of view. Different dosage schedules should be tested to determine whether this factor influences the frequency of response. These studies will require a protocol.

The last paragraph of Osserman's letter is most disturbing, for it implies that a rigid protocol interferes with the proper medical management of patients. If this were the case, cooperative group studies would be unethical. The SWCCSG and other cooperative study groups take great care to emphasize optimum supportive care in addition to the study drug. The protocols employed are rigid only in the sense that the study plan must be such that the effectiveness of the study drug or dosage schedule can be evaluated; it is inconceivable that a study protocol would prevent investigators from using the important supportive measures mentioned in Osserman's letter. We have found that patients are investigated more completely, seen more frequently, and probably receive more enlightened general care now than they did before study protocols were introduced into our institutions.

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Changes in the Tail Feathers of the Adolescent Lyrebird

Since the publication of my report on the changes which occur in the tail feathers of the adolescent lyrebird, *Menura superba* [*Science* **147**, 510 (1965)], evidence has been obtained which renders it necessary to correct a statement on page 512 (near the top of column 2) of that report regarding the development of the two central feathers (medians). It is now clear that these feathers progress from the juvenile to the mature form by a series of moults and replacements and not by transformation of the juvenile vaned feathers into the adolescent medians.

It is also apparent that the other vaned feathers undergo changes in form (by moulting and replacement) as the bird matures. Recently the almost complete tails were recovered from two birds which had been killed by predators. One bird was in its first or early in its second year, while the other was in its third or fourth year. Though one of the medians was broken, the differences between the plain feathers and between the medians of the two birds are clearly visible. Photographs are available.

The filamentation process whereby plain vaned feathers are converted into or replaced by filamentaries, which was described in the previous report, begins at a later stage.

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